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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,950	09/30/2005	Timothy P. Tully	17VV-137227	1059

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
08/10/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,950	TULLY ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,12-15,17-22,24 and 25* is/are pending in the application.

4a) Of the above claim(s) *17,18 and 25* is/are withdrawn from consideration.

5)☒ Claim(s) *12-15,19-22 and 24* is/are allowed.

6)☒ Claim(s) *1-4 and 6-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment filed on 20 April 2010 has been entered into the record and has been fully considered. Claims 1-2, 7-8, 12-13, 19 and 24 have been amended.

2. Claims 1-4, 6-10, 12-15, 19-22 and 24, drawn to a method of identifying candidate compounds for enhancing CREB pathway function and assessing the effect on CREB-dependent gene expression, are under consideration in the instant application.

Response to Amendment

Withdrawn objections and/or rejections

3. Upon consideration of the Applicant's submission of the cover page of the Journal of Molecular Neuroscience (August-October 2002) (Exhibit A) displaying a date stamp of the relevant issue (having the Scott article) from the University of Oregon Library as to when the article was publicly available, the rejection under 35 USC § 102(a) is withdrawn. The date on the cover page was September 4, 2002, i.e. after the priority date (8/19/2002) of the instant invention.

4. Upon consideration of invalidity of the rejection over the Scott article for being post-dated, the rejection of claims under 35 USC § 103(a) using the Scott reference is withdrawn.

5. Upon consideration of claim amendments, the rejection of claims under 35 USC § 112, second paragraph, is withdrawn.

Rejections maintained

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The rejection of claims 1, 7-10, 12-15, 19-22 and 24, under 35 U.S.C. 112, first paragraph, **is applied to amended claims 1, 7-10,** for reasons of record in the Office Action dated 20 January 2010. Applicant's amendment of claims to recite "significantly increased" and "forskolin" have been persuasive for the withdrawal of the 112, 1st paragraph rejection over claims 12-15, 19-22 and 24.

However, claims 7-10 and independent claim 1 stay rejected because the specification, while being enabling for a method for identifying a candidate compound for enhancing cyclic AMP response element binding protein (CREB) pathway function by contacting host cells/cells of neural origin with a test compound and forskolin, wherein the indicator activity/CREB dependent gene expression in cells treated with forskolin

and test compound is significantly increased versus that observed with cells plus forskolin alone, does not reasonably provide enablement for the identification of a candidate compound following the same steps resulting in **any difference** in CREB dependent gene expression between the groups as stated above (see claims 7-10, particularly 7(m)) (emphasis added).

7. As stated in the previous Office Action, it is repeated that the specification of the instant application teaches that the CREB dependent gene expression in cells treated with a CREB function stimulating agent (forskolin) and a test compound is "statistically significantly increased relative to the endogenous CREB-dependent gene expression in the control cells", wherein the control cells are represented by cells treated with forskolin alone (para 0008). However, the specification does not teach that the observation of <u>any difference</u> (an increase or a decrease) (emphasis added) in CREB dependent gene expression would indicate that the compounds are CREB pathway function enhancers as claimed. Undue experimentation would be required of a skilled artisan to identify a candidate compound that will enhance CREB function by eliciting any difference (increase or decrease, significant or non-significant) in CREB dependent gene expression, with a reasonable amount of success and predictability. The specification must provide such guidance commensurate in scope with the claims. The breadth of "a difference" in

the CREB dependent gene expression in cells with or without test compound, constitute an invitation to experiment by trial and error.

8. The Examiner set forth a reasonable explanation of why the claimed invention is not adequately enabled by the specification's description of the invention (page 4-9 of the Action of 1/20/2010). Specifically, proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to identify a candidate compound for enhancing CREB pathway function by obtaining any difference in the CREB dependent gene expression, the lack of direction/guidance presented in the specification; the absence of working examples directed to same; the complex nature of the invention; and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention. It is suggested that amending claim 7 (m) to recite "significant increase" would overcome this rejection.

New Rejections

Claim Rejections - 35 USC § 112-Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 7(m) is vague and unclear for reciting the limitation "a difference". The instant specification teaches statistically significant increased gene expression (see para 0008). It is not clear if the difference should be significant or can be non-significant as well. Appropriate correction/clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the

examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 3-4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ying et al. (JBC 272: 2412-2420, 1997 – listed in IDS), in view of Tully et al (WO 96/11270, dated 4/18/1996 – listed in IDS), and in further view of Shoemaker et al (Can Res 45, 2145-2153, 1985).

13. The claims are directed to a method of identifying candidate compounds for enhancing CREB pathway function, (i) by contacting host cells comprising an indicator gene linked to a CRE promoter with a test compound and CREB function stimulating agent (forskolin); (ii) determining the indicator activity and comparing the same in the above cells versus control cells contacted with the CREB function stimulating agent alone; (iii) selecting the test compound if the indicator activity in cells treated with CREB function stimulating agent and test compound is increased relative to the above control cells; (iv) selecting the test compound if the indicator activity in control cells treated with test agent is not significantly different from the activity elicited by control cells not treated with any agent; (v) repeating the above steps with a range of concentrations of the test agent; wherein the host cells are neuroblastoma cell, and the indicator gene is luciferase (claims 1, 3-4, 6).

14. Ying et al. teach that host cells (Calu-6 or human lung cancer cells) were transiently transfected using plasmids comprising the HREN promoter having the consensus CRE sequence (e.g. 900L, 900CRE, etc.)

(Table 1; Figure 1), luciferase indicator gene, and expression vector encoding the CREB-1 transcription factor (abstract) and contacted with forskolin (Materials and Methods, page 2413, col 2, para 2). The reference further teaches that the luciferase activity elicited by cells transfected with reporter constructs such as 900CRE, and contacted with CREB expression vector along with forskolin is significantly increased with respect to cells without the CREB expression vector. Additionally, the cells not treated with forskolin and CREB expression vector are not significantly different than cells in contact with CREB expression vector alone (Figure 6A).

Please note that the CREB vector can function as a CREB analog to enhance CREB function, therefore is interpreted as having the same properties of the claimed test compounds.

15. Ying et al. do not teach repeating the method steps with a range of concentrations of the test compound and the screening of a plurality of compounds that would enhance CREB function.

16. Tully et al. teach screening assays of pharmaceutical drugs for enhancing long-term memory by activating CREB or CREB isoforms (page 4, para 4; page 5, para 2).

17. Ying et al. or Tully et al. do not teach repeating the method steps using different concentrations of the test compound.

18. Shoemaker et al. teach drugs for screening assays for different tumor types including neuroblastoma cells (page 2149, Table 3).

Shoemaker et al. also teach that after the primary or initial screening steps of identifying test compounds, dose response assays involving 10-fold dilutions (or different concentrations) of test compound was performed (page 2146, col 1, Drug Treatment, Materials and Methods). The reference further teaches that the complete evaluation of active compounds will involve 5-dose response experiments (i.e. will include four different concentrations as in instant claim 6) using the assay steps (or repeating the steps done with the original concentration), for determining the minimum effective concentration of the test compound (page 2150, col 1, para 2).

19. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the in vitro CREB activating assay for screening of pharmaceutical agents for enhancing long term memory as taught by Ying et al. and Tully et al., by repeating the assay steps using different concentrations of the identified test compound in view of the teachings of Shoemaker et al. The person of ordinary skill in the art would have been motivated to perform a dose response curve using different concentrations of the test compound, as this would confirm the activity obtained by the original concentration, define the spectrum of the desired activity, and derive at a minimum effective concentration of the test compound (Shoemaker et al. col 2, para 2). The person of ordinary skill in the art would have expected success because in vitro cell based assays using one or more agents were

routinely performed in the scientific and medical community, at the time the invention was made.

20. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

21. Claims 1-4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ying et al. (1997), in view of Tully et al (1996), and in further view of Shoemaker et al (1985).

22. Claim 2 recites that the host cells are contacted with the test/candidate compound prior to contact with the CREB function stimulating agent.

23. The teachings of Ying et al., Tully et al. and Shoemaker et al. are set forth above.

24. Ying et al., or Tully et al. or Shoemaker et al. do not teach that the host cells are contacted with the test/candidate compound prior to contact with the CREB function stimulating agent.

25. However, since the disclosure does not specify criticality of the claimed time of addition of the test compound, optimization within prior art conditions or through routine experimentation is obvious to one skilled in the art. In the case of contacting the host cell with the test compound prior to forskolin, one of skill in the art would clearly recognize addition of compounds must be timed sufficiently to obtain an optimum activity of the

compound. As such, the timing of the addition of the compound in an assay would amount to nothing more than routine experimentation that can be optimized.

As stated in MPEP 2144.05:

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382; Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 UDPQ2d 1843 (Fed. Cir.).*

26. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to determine the optimal time for contacting the test compound with the host cell for optimizing the screening assay and determining a test compound that would enhance the CREB pathway function, in view of the combined teachings of Ying et al., Tully et al. and Shoemaker et al. The person of ordinary skill in the art would have been motivated to perform such tests and would have expected success because of the involvement of CREB pathway in multiple biological and cognitive functions.

27. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

28. Claims 12-15, 19-22 and 24 are allowable.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
31 July 2010

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649